15. (Currently Amended) The method of Claim ~~28~~ 29, wherein the outlet has an exposed height of about 0 to 300 ~~mm~~ μm.

16. (Currently Amended) The method of Claim ~~28~~ 29, wherein the delivery rate or volume is controlled by spacing of multiple needles, needle diameter or number of needles.

17-24. Withdrawn.

25-28. Canceled.

29. (Previously Presented) A method for administration of a substance to a human subject, comprising delivering the substance into an intradermal compartment of the human subject's skin, so that the substance is distributed systemically and has a pharmacokinetic profile similar to subcutaneous delivery of the substance, but with a higher plasma level.

30-31. Canceled.

## REMARKS

Claim 29 is resubmitted for examination, and claims 28, 30, and 31 have been canceled without prejudice to the Applicants' right to pursue the subject matter of the canceled claims in one or more related applications. These claims have been canceled merely to limit the issues and expedite prosecution of the remaining claims. Thus, rejection of these claims are obviated and should be withdrawn. Claims 10-13, and 15 have been amended to correct the informalities relating to the recitation of "mm", where "μm" was required. Claims 2-6, 10-16 have been amended to delete dependencies from claims canceled upon entry of the instant amendment.

After entry of this amendment claims 2-7, 10-16, and 29 will be pending in the application.

## 1. INTERVIEW SUMMARY

Applicants would like to thank Examiner Hayes for the telephonic interview of December 19, 2003 with Applicants' representatives Laura Coruzzi and Paki Banky in connection with the outstanding Office Action. During the telephonic interview, the outstanding Office Action and the pending claims were discussed. The substance of the interview and reasons for patentability of the claims is addressed in detail below.

## 2. RESTRICTION/ELECTION OF CLAIM 29

Applicants assert that claims 29-31 are appropriately examined in the instant application as these claims are directed to an elected invention. In particular, Applicants had elected to pursue claims drawn to a method of delivering a substance into skin in response to a restriction requirement issued at the commencement of examination (*See* Office Action mailed 4/26/02; pursuant to a telephonic interview with Applicants' representatives on April 2, 2002, a provisional election was made to prosecute claims directed to a method of delivering a substance into skin). Claims 25-30 were then added as part of the elected subject matter (Amendment dated October 28, 2002), and were, indeed examined (Office Action dated January 14, 2003). Applicants believe that the recent restriction of these claims is in error and should be withdrawn. During the interview, the Examiner indicated that the requirement for restriction would be maintained, but that Applicants would elect and resubmit *any one* of claims 29-31 for examination. In order to expedite prosecution, Applicants have canceled claims 28, 30, and 31, without prejudice to pursue the subject matter of the canceled claims in one or more related applications, and have elected to pursue claim 29 for prosecution on the merits.

## 3. THE REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 2-7, 10-16, and 28 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and use the claimed invention. Specifically, the Examiner contends that there is no enabling disclosure for delivery of a substance at a controlled rate and volume as recited in claim 28. Applicants respectfully disagree and contend that the parameters taught in the specification, including the working examples provide ample guidance to enable the skilled artisan to make and use the claimed invention without undue experimentation. However, in view of the present claim amendments, the Examiner's rejection is moot and should be withdrawn.

## 4. PENDING CLAIMS SATISFY THE ENABLEMENT REQUIREMENT

Claim 29 and claims dependent therefrom relate to a method for administration of a substance to a human subject, comprising delivering the substance into an intradermal

compartment of the human subject's skin, so that the substance is distributed systemically and has a pharmacokinetic profile similar to subcutaneous delivery of the substance, but with a higher plasma level. These claims are not rejected under 35 U.S.C. § 112. Nevertheless, the Applicants take this opportunity to explain why claim 29, and claims dependent therefrom, are enabled as of the filing date of the instant application.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, *without undue experimentation*, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). The instant specification satisfies the enablement requirement, in that the disclosure in the specification coupled with information known in the art at the time the application was filed allows one skilled in the art to make and use the claimed invention without undue experimentation.

The instant specification, coupled with information which was readily available to the skilled artisan at the time the instant application was filed, provides a disclosure which fully enables the claimed invention, *i.e.*, delivery of a substance to the intradermal compartment. Applicants respectfully point out that the specification as originally filed provides ample guidance for delivering a substance into an intradermal compartment of a human subject's skin, so that the substance is distributed systemically and has a pharmacokinetic profile similar to subcutaneous delivery of the substance, but with a higher plasma level. The basic teachings of the invention as set forth in the instant specification include the following:

1. <u>*Needle Length and Geometry*</u>: The instant specification sets forth principles and parameters that ensure targeting the intradermal compartment, *e.g.*, *see*, discussion relating to needle length and configuration of its outlet to prevent unwanted leakage. In the "Detailed Description of the Invention", Applicants teach the importance of the length of the needle and the relative exposed height of the needle outlet for targeting the intradermal compartment (*see* instant specification at p. 4, *l.* 29 to p. 5, *l.* 21). The specification describes the use of microneedles that have <u>*both*</u> a *length* sufficient to penetrate the intradermal space and an *outlet* at a depth within the penetration space to allow the skin to seal around the need to prevent effusion of the substance onto the surface of the skin due to backpressure. (*See* the instant specification at p. 5, *ll.* 6-10). Example 1 exemplifies the

teachings of the invention by using specific needles of a defined length and geometry for intradermal delivery of insulin and PTH. The needle used is a stainless 30 gauge needle bent at the tip at a 90° angle such that the available length for skin penetration is 1-2 mm. The needle outlet is at a depth of 1.7-2 mm in the skin when the needle is inserted and the total exposed height of the needle outlet is 1.0-1.2 mm. Thus, one skilled in the art provided with the instant application would know that needles having the correct length and outlet depth are one of the fundamental principles of the teachings of the instant invention for delivering the substance to the intradermal compartment of a subject's skin so that the substance is distributed systemically with a specific pharmacokinetic profile.

2. *Pressure*: Applicants have for the first time solved the problems associated with delivery to the intradermal compartment resulting from backpressure exerted by the skin and the pressure build up from accumulating fluid. The specification describes mechanisms that can be used to provide adequate pressure to achieve efficient and consistent delivery of a substance to the intradermal compartment and systemic distribution of that substance. According to the guidelines set forth in the "Detailed Description of the Invention", in order to achieve intradermal delivery of a substance, a *constant pressure* needs to be applied *directly on the liquid interface* to provide a constant delivery rate, which is essential for optimal systemic absorption. (*See* instant specification at p. 5 , *l.* 22 to p. 6, *l.* 6). Example 1 exemplifies how Applicants have solved problems associated with controlling backpressure exerted by the skin and the pressure build up from accumulating fluid, by referring one skilled in the art to the teachings of U.S. Patent No. 5,957,895 (a copy of which is provided herewith as Exhibit A for the Examiner's convenience) whereby configurations of pressure controlling devices, specifically with Belleville spring diaphragms are disclosed to deliver a substance at a constant pressure, without the need for a pump. Therefore, one skilled in the art provided with the instant specification and guided by the knowledge available in the field of drug delivery (such as U.S. Patent No. 5,957,895) at the time of filing would appreciate the need to apply the teachings of the specification to control pressure to achieve delivery of a substance to the intradermal compartment of a subject's skin in accordance with the invention as claimed.

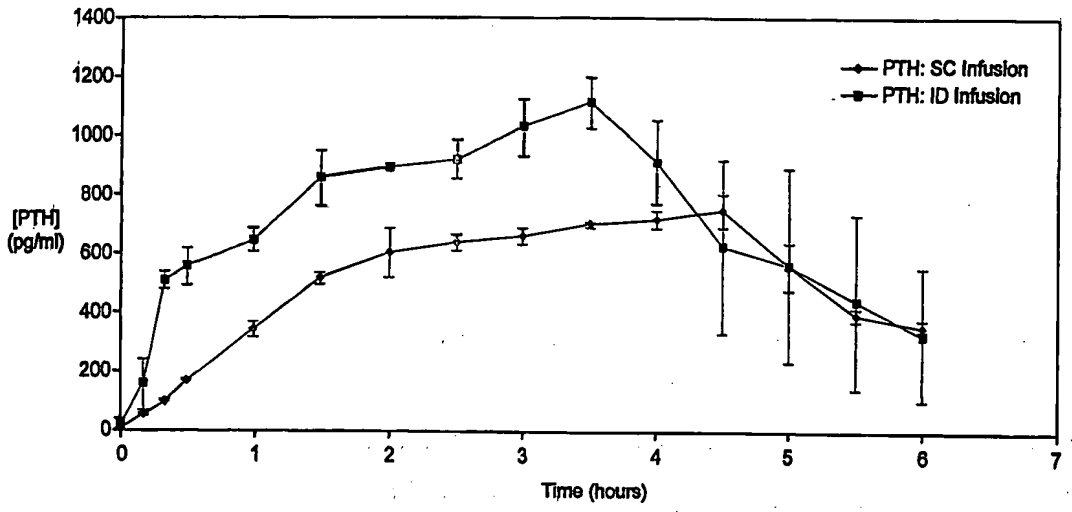
3. *Rate and Volume of Delivery*: The instant specification sets forth the criticality of controlling delivery rates to prevent the formation of weals at the site of delivery

and to prevent backpressure from pushing the needle out of the skin. The instant specification provides examples whereby desired delivery rates and volumes may be achieved. An exemplary method by which the delivery rates are controlled as set forth in the instant specification is by varying the size and number of microneedles and the spacing between them (*See* the instant specification at p. 5, *l.* 27 to p. 6, *l.* 6). As a result, one skilled in the art provided with the instant specification would know that the appropriate delivery rates and volumes may be determined *without undue experimentation*. Undue experimentation is one that requires a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (CCPA 1971). The factors taken into account in this determination include, the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature, and the level of skill in the art. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). By this standard, determining the appropriate delivery rates and volumes is by no means undue, and undoubtedly within the level of ordinary skill in the art. In fact, Example 1 exemplifies how delivering a substance such as insulin and PTH at a controlled volume and rate would result in intradermal delivery and systemic absorption. Therefore, one skilled in the art provided with the instant specification and guided by his knowledge and skill in the art would appreciate the requirement of controlling the rate and volume of delivery and would know how to determine the appropriate rate and volume of delivery with routine experimentations.

Example 1 is an embodiment of the application of the principles and guidelines of the instant invention, whereby PTH is delivered to the intradermal compartment of a pig's skin [1] and is distributed systemically having a pharmacokinetic profile similar to subcutaneous delivery of PTH, but with a higher plasma level. Specifically, PTH is delivered using a needle of *appropriate length and outlet depth* in accordance with the teachings of the invention, *i.e.*, a 30G bent needle with an outlet depth of 1.7-2.0 mm having an exposed height of 1-1.2 mm, such that the available length for skin penetration is 1-2 mm. PTH is delivered at a *controlled rate and volume* while the *pressure of delivery is controlled* using

[1] The teachings of the instant invention is exemplified in a pig animal model because it is the prototypic model for human skin as acknowledged by those skilled in the art since the thickness of the pig's various skin compartments most closely approximates human skin.

commonly used pumps, *i.e.*, at a rate of 75 μL/hr; wherein the flow rate is controlled by a Harvard syringe pump. The results are shown in Figure 3, where plasma PTH levels, subsequent to intradermal administration are plotted over time to generate a serum concentration-time curve, *i.e.*, its pharmacokinetic profile (PK), which is concurrently compared to the PK profile observed for subcutaneous administration of PTH (for the Examiner's convenience, Figure 3 from the instant application is reproduced below).




It is clear from a visual inspection of Figure 3, that the PK profile of PTH delivered to the intradermal space is similar to that of SC, but differs in that it has a higher plasma level; *i.e.*, delivering to the intradermal space results in approximately 325 pg/mL units higher serum concentration of PTH throughout the infusion as compared to SC administration. Therefore, the application of the principles of the invention result in delivery of PTH to the intradermal compartment so that the substance is systemically distributed with a PK profile similar to SC but with a higher plasma level.

In view of the foregoing, one skilled in the art working in the field of drug delivery, provided with the instant specification would know how to deliver a substance to the intradermal compartment of a subject's skin so that the substance is distributed systemically with a pharmacokinetic profile similar to subcutaneous delivery of the substance, but with a higher plasma level. One skilled in the art working in the field of drug delivery would know that to deliver a substance to the intradermal compartment of a human subject's skin, the length and configuration of the needle, the pressure of the delivery, and the rate and volume of the delivery need to be carefully controlled to achieve the desired effect, *i.e.*, a

pharmacokinetic profile similar to subcutaneous delivery of the substance, but with a higher plasma level.

**5. THE REJECTION UNDER 35 U.S.C § 102(e) SHOULD BE WITHDRAWN**

Claims 28, 2-7, 10-11, and 16 are rejected under U.S.C. § 102(e) as being allegedly anticipated by Allen *et al.*, (U.S. Patent No. 6,334,856; "Allen"). Allen describes *epi*dermal, transport and, therefore, does not anticipate the claims. Nevertheless, in view of the present claim amendments, the Examiner's rejection is moot and should be withdrawn.

However, Applicants, take this opportunity to clarify for the record that the presently claimed invention is not anticipated. Allen does not describe delivering a substance into the intradermal compartment of a subject's skin to achieve systemic distribution and a pharmacokinetic profile similar to subcutaneous administration but with a higher plasma level and as such cannot anticipate the claimed invention.

Allen relates to methods and devices for transporting a substance across the stratum corneum, *i.e.*, the outermost impermeable barrier of the skin. The devices disclosed in Allen are designed to have needles of such lengths and configurations that can at most penetrate the epidermal compartment of skin. Allen teaches away from delivering a substance into the dermis and provides parameters whereby the penetration depth is deliberately limited to the epidermal compartment of skin (*see* Allen at col. 9, *ll.* 2-16). The methods and devices disclosed in Allen do not target the intradermal compartment and thus do not achieve the benefits of the claimed invention, *i.e.*, systemic distribution of the substance and a pharmacokinetic profile similar to SC administration but with a higher plasma level.

Allen relates to delivery of a substance *solely* across the outermost barrier of skin and does not describe delivery *past the epidermis into the intradermal compartment*, and thus cannot anticipate the claimed invention. Even the examiner recognizes that Allen discloses a method of delivering insulin, growth hormones, and other drugs using a needle or a plurality of needles that has a length of a range of 1 um to 1 mm to attain a delivery depth of 0-100 μm so that the delivery depth does not penetrate past the epidermis (*see* page 4 of the Office Action mailed November 24, 2003). The Examiner points to Allen wherein devices disclosed are designed to simply penetrate the stratum corneum of the skin, into the epidermis, without *penetrating past the epidermis, i.e., they do not penetrate the dermis* (*see* Allen column 9, *ll.*

4-9)[2]. The present invention, unlike Allen discloses a method for delivering a substance past the epidermis, into the intradermal space so that the substance is distributed systemically.

Thus, in view of the foregoing, Allen does not anticipate the claimed invention and the rejection should be withdrawn.

## 6. THE REJECTION UNDER 35 U.S.C §103(a) SHOULD BE WITHDRAWN

Claims 12, 13, 14, and 15 are rejected under 35 U.S.C §103(a) as being unpatentable over Allen in view of Waitz *et al.*, (U.S. Patent No. 5,484,417; "Waitz"). The rejection of the claims as made obvious over Waitz in view of Allen is in error and should be withdrawn. A careful review of these references reveals that intradermal delivery and systemic distribution of a substance is not suggested nor made obvious by the references taken alone or in combination.

The Examiner erroneously contends that Allen discloses a method of delivering a substance to the intradermal compartment, and that one of ordinary skill in the art would have been motivated from the teachings of Allen to increase the outlet depth in order to account for the thicker stratum corneum and the epidermis by looking at teachings of Waitz.

As described above, Allen provides methods and devices for transporting a substance across the stratum corneum into the epidermis, without passing the dermis. By contrast, the pending claims relate to delivering a substance into the intradermal compartment of a subject's skin so that the substance is systemically distributed with a desired pharmacokinetic profile. Waitz does not cure the deficiencies of Allen. Waitz does not teach or even suggest a method or a device for delivering a substance to skin, let alone into the intradermal compartment. Waitz relates to cannulas for delivering fluids to blood vessels, ducts, or other hollow organs, *not skin*. Thus, there is no clear and particular teaching, suggestion or motivation found in either reference to combine the two. Without evidence of the requisite teaching, suggestion or motivation to combine the references, Waitz and Allen cannot be used to make a *prima facie* case of obviousness. *In re Lee*, 277 F 3d. 1341. Therefore, Allen

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[2] The Examiner erroneously characterizes Allen as describing a method for delivering a substance to the *intradermal compartment*, however, by his own admission the parameters provided in Allen are merely sufficient to deliver the substance to the epidermis. (See p. 4 of the Office Action). A careful reading of Allen indicates that there is no disclosure relating to delivering a substance to the intradermal compartment. It is incorrect and improper to attribute the teachings of the applicant's own teachings into the prior art for purposes of anticipation.

in view of Waitz does not render claims 12, 13, 14, and 15 obvious, and Applicants thus respectfully request that the rejection be withdrawn.

## CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an early allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted, by Jacqueline Benn
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